INBORN ERRORS OF IMMUNITY

What are inborn errors of immunity?

Inborn errors of immunity (IEI) also known as Primary Immunodeficiency Diseases (PID) refers to a heterogenous group of inherited disorders with defects in one or more components of the immune system. There are more than 400 hundred different types of IEI reported till date.

How do they occur?

These disorders can be inherited in an autosomal recessive, autosomal dominant, and X-linked recessive manner. Genetic basis of few inborn errors of immunity has not been elucidated yet.

What are different types of inborn errors of immunity?

IEIs can be broadly classified into the following categories: cell-mediated, predominantly antibody deficiency, combined antibody and cell mediated defects, phagocyte, complement pathway, and other well-characterized immunodeficiency syndromes.

What are the clinical manifestations of Inborn errors of immunity?

Recurrent and severe infections are the most common manifestations. Patients may present with recurrent pneumonia, diarrhoea, skin infections and deep-organ abscesses. A significant proportion of patients may also present with immune dysregulations in the form of autoimmunity (abnormal immune response against self) and allergies. Common autoimmune manifestations include arthritis, rash, cytopenias. Malignancy, particularly of the hematopoietic system can also occur in some IEIs. The manifestations range in severity from life-threatening disorders presenting in infancy to less severe disorders diagnosed in adulthood.

How are IEIs diagnosed?

A tiered approach is used for the diagnosis of these disorders and includes simple laboratory investigations such as complete blood count, estimation of immunoglobulins and complements along with more specialized tests. DNA based tests are needed for confirmation of diagnosis and genetic counselling.

Common forms of inborn errors of immunity

Antibody deficiencies are one of the most common inborn errors of immunity. Patients with antibody defects lack one or more or all types of immunoglobulins in their blood due to defect in development and maturation of B lymphocytes. Patient with antibody deficiencies present with recurrent respiratory tract or gastrointestinal tract infections. They can also develop severe infections with enteroviruses including central nervous system infection. Vaccine associated paralytic poliomyelitis is another concern in these patients.

X-linked agammaglobulinemia (XLA) is a prototypic antibody deficiency predominantly affecting male children. Severe combined immunodeficiency (SCID) and phagocytic defects such as chronic granulomatous diseases (CGD) are some other common IEIs.

What are the treatment options for inborn errors of immunity?

Management of IEI differs across the spectrum of severity and depends largely on the specific type of IEI. A combination of the following modalities of treatment are used for management of different IEIs**.**

A. MEASURES TO PREVENT INITIAL INFECTIONS

1. Immunoglobulin replacement therapy

2. Antimicrobial prophylaxis

B. ESTABLISHING IMMUNE RECONSTITUTION

1. Hematopoietic stem transplantation (HSCT)

2. Gene therapy

3. Thymic transplants

4. Enzyme replacement and metabolic therapies

C. TREATMENT OF COMPLICATIONS

1. Treatment of infections with antimicrobials

2. Treatment of autoimmunity and malignancy using immunomodulatory therapies like corticosteroids and biologicals

Immunoglobulin replacement therapy

Replacement of immunoglobulin is used in a variety of IEIs, including primary antibody deficiencies, severe combined immune deficiency and combined immunodeficiencies until B cell function is restored. Immunoglobulin can be replaced intravenously (IVIg) or subcutaneously (SCIg). SCIg formulations have been recently marketed in India.

What is the current cost of replacement IVIg?

IVIg is an expensive drug as it is obtained from human plasma. At present the market price of IVIg in the country is approximately INR 8500 / 5 gm. The dose of the drug, and hence cost of

therapy, depends on the weight of the child . For a 10 kg child cost would be INR 8500 per month and is life long.

How can IEIs be cured and immune reconstitution be established in a patient?

Immunologic reconstitution may be possible in several types of IEIs in the form of hematopoietic cell transplantation (HCT), enzyme replacement, thymic transplantation, or gene therapies.

Hematopoietic stem transplantation (HSCT)

HSCT has been used as the primary curative therapy for severe forms of IEIs. HSCT is the treatment of choice for most cases of SCID and is also a treatment option for several other forms of IEIs including many combined immunodeficiencies. Improvements in HSCT procedures and supportive care have resulted in better outcomes.

Several factors influence the consideration of HSCT for IEIs. These include underlying diagnosis, patient health status, donor options, local transplant center practice preferences and experience, and family understanding and willingness. Approximate cost of hematopoietic stem cell transplantation (HSCT) in India is 15-20 lakhs

When are biological agents other targeted therapies used in treatment of various IEIs?

Many autoinflammatory syndromes are treated using interleukin-1 receptor antagonist (Anakinra). It is an expensive drug and is not yet marketed in India. It must be imported on a named patient basis**. The cost Is approximately INR 2.5 lakh**

What are the long-term outcomes following treatment?

IEIs are potentially life-threatening disorders. Several medical therapies have provided dramatic improvements in life expectancy and quality of life for patients with IEIs.

HSCT is the only potentially curative therapy available for SCID. Survival rates have continued to improve with early diagnosis, advances in the methods of preparing hosts and donor cells, and in supportive and adjuvant therapies.

Patients with predominantly antibody deficiency need to be treated with IVIg lifelong. Children who are diagnosed early and receive appropriate treatment do well on follow up and can look forward to a good quality of life and become useful members of the society as adults. However, if these individuals are denied access to this therapy, the consequences can be grave as mortality rates are, unfortunately, very high.